Multivitamins, Individual Vitamin and Mineral Supplements, and Risk of Diabetes Among Older U.S. Adults

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OBJECTIVE — Understanding the relationship between multivitamin use and diabetes risk is important given the wide use of multivitamin supplements among U.S. adults.

RESEARCH DESIGN AND METHODS — We prospectively examined supplemental use of multivitamins and individual vitamins and minerals assessed in 1995–1996 in relation to self-reported diabetes diagnosed after 2000 among 232,007 participants in the National Institutes of Health–American Association of Retired Persons Diet and Health Study. Multivitamin use was assessed by a food-frequency questionnaire at baseline. Odds ratios (ORs) and 95% CIs were calculated by logistic regression models, adjusted for potential confounders. In total, 14,130 cases of diabetes diagnosed after 2000 were included in the analysis.

RESULTS — Frequent use of any multivitamins was not associated with risk of diabetes after adjustment for potential confounders and uses of individual supplements. Compared with nonusers of any multivitamins, the multivariate ORs among users were 1.07 (95% CI 0.94–1.21) for taking vitamins less than once per week, 0.97 (0.88–1.06) for one to three times per week, 0.92 (0.84–1.00) for four to six times per week, and 1.02 (0.98–1.06) for seven or more times per week (P for trend = 0.64). Significantly lower risk of diabetes was associated with the use of vitamin C or calcium supplements. The multivariate ORs comparing daily users with nonusers were 0.91 (0.86–0.97) for vitamin C supplements and 0.85 (0.80–0.90) for calcium supplements. Use of vitamin E or other individual vitamin and mineral supplements were not associated with diabetes risk.

CONCLUSIONS — In this large cohort of U.S. older adults, multivitamin use was not associated with diabetes risk. The findings of lower diabetes risk among frequent users of vitamin C or calcium supplements warrant further evaluations.

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Multivitamin supplements contain large amounts of many vitamins and minerals that approximate or exceed the recommended micronutrient intakes. With the relative safety and inexpensiveness, multivitamins are the most commonly used dietary supplements in the U.S. and are advocated as an attractive option for preventing chronic diseases, such as cancer, cardiovascular disease, and type 2 diabetes (1,2). Approximately 50% of U.S. adults routinely take multivitamins and spend ~$23 billion annually (1).

Type 2 diabetes is considered to be the epidemic of the 21st century, and its prevalence in the U.S. is growing rapidly (3). Given the rising health burden of type 2 diabetes and its complications, there is a great urgency to develop effective strategies for curbing this trend. Dietary supplements such as multivitamins have been commonly used for disease prevention. Evidence from basic research and observational studies has suggested that adequate intake of antioxidant vitamins or minerals may protect against the development of type 2 diabetes via reduction of oxidative stress and its associated metabolic abnormalities, including systemic inflammation, endothelial dysfunction, hypertension, and dyslipidemia (1,2,4,5). These metabolic abnormalities act individually or synergistically to impair pancreatic β-cell insulin secretion and interfere with glucose disposal in peripheral tissues (6) and thereby accelerate the development and progression of both atherosclerosis and type 2 diabetes. However, available epidemiological data on micronutrients and diabetes that focused on individual vitamin/antioxidant supplements have yielded inconsistent results.

With their popularity, multivitamin supplement use contributes to a considerable proportion of micronutrient intake among users and sometimes excessive intakes of certain micronutrients in some subgroups of the population (2). There is a longstanding interest in the diabetes research community regarding the potential, yet unproven, benefits or risks of multivitamin use on the development and progression of type 2 diabetes. We therefore prospectively evaluate the association between the use of multivitamins or individual micronutrient supplements and diabetes risk in a large cohort of older adults in the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study.

RESEARCH DESIGN AND METHODS

— The NIH-AARP cohort was established in 1995–1996 by the National Cancer Institute to investigate the roles of diet and lifestyle in cancer etiology (7). Cohort participants included 566,402 AARP members aged 50–71 years in 1995–1996 from six states (California, Florida, North Carolina, Pennsylvania, New Jersey, and Louisiana) and

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two metropolitan areas (Atlanta and Detroit). All study participants completed a comprehensive dietary survey that included a 124-item food-frequency questionnaire and a short survey on demographics, medications, and lifestyle (7). A follow-up questionnaire was mailed out to surviving participants of the original cohort in 2004–2006 to update exposures and to ascertain the occurrences of major chronic diseases, including diabetes. A total of 318,261 participants responded to the follow-up survey and were therefore eligible for the present study. We excluded 21,632 participants who provided no or inconsistent information on multivitamin use and 31,383 participants with missing values on diabetes diagnosis. Because vitamin supplement use was assessed in 1995–1996, to reduce the possibility that diabetes itself might have affected health behaviors, we further excluded 33,239 diabetic patients who reported a diabetes diagnosis before 2000. Therefore, the final analytic sample included 232,007 participants, 217,877 without diabetes and 14,130 diabetic case subjects diagnosed after 2000.

Assessment of vitamin supplement use

As part of the baseline dietary survey, participants were asked whether they took any vitamins or minerals in the past 12 months with three categorical choices (no, less than once per month, and once or more per month). For those who took vitamins once or more per month, we further asked for the frequencies of use for three types of multivitamins (stress-tab type, therapeutic or theragran type, and one-a-day type). Five categorical answers were allowed for each of these multivitamins (times/week): never, less than one, one to three, four to six, and daily. In addition to multivitamins, we also asked for the use of vitamin A, β-carotene, vitamin C, vitamin E, and calcium (including Tums) with the same categorical frequencies. Finally, participants were asked whether they took several other individual vitamins and minerals more than once per month, including iron, zinc, selenium, and folic acid. For individual vitamins and minerals, we instructed participants not to include vitamins and minerals contained in multivitamins that they had reported in the multivitamin section.

In addition, the baseline survey also collected data on basic demographics and lifestyle such as date of birth, sex, race, education level, marital status, smoking habit, and physical activity. Consumption of coffee and alcohol and dietary intakes of calories and micronutrients were derived from the food-frequency questionnaire. Finally, participants were asked to self-evaluate their health status as excellent, very good, good, fair, or poor and to report weight in pounds (0.45 kg) and height in inches (2.54 cm). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Ascertainment of diabetes

A question on lifetime occurrence of physician-diagnosed diabetes was first asked at the dietary survey in 1995–1996. This information was updated on the follow-up questionnaire in 2004–2006, along with the year of first diagnosis in the following categories: before 1985, 1985–1994, 1995–1999, or 2000 to present. These questions did not differentiate type 2 from type 1 diabetes; however, in adults, ~90–95% of all diagnosed diabetes is type 2 diabetes. Because the current study included only older adults and adults with incident cases of diabetes diagnosed after 2000, we believe that most of diabetes cases in the current analysis should be type 2 diabetes.

Statistical analysis

To minimize the possibility that diabetic patients modified their lifestyle around or after the diagnosis, the current analysis only included incident diabetes cases diagnosed after 2000, at least 4–5 years after the exposure assessment. The frequency for overall multivitamin use was calculated by adding up the use of individual types of multivitamins. In the analysis, the frequency of supplement use was defined as (times/week) never, less than one, one to three, four to six, and daily. No frequency data were collected for supplemental uses of iron, zinc, selenium, and folic acid, and, thus, only yes/no variables were included in the analysis. We performed *t* tests or ANOVA for continuous covariates and χ^2 tests for categorical covariates to formally test the differences of covariates between nonusers and all users as well as among four categories of users only. Multivariate odd ratios (ORs) and 95% CIs were derived from logistic regression models. Potential confounders included age in year, sex, race (whites versus nonwhites), education level (<8 years, 8–11 years, 12 years or completed high school, post–high school or some college, college and postgraduate), marital status (married or living as married, widowed, divorced, separated, or never married), smoking status (never smokers; past smokers with years since last smoking: ≤35, 30–34, 20–29, 10–19, or 1–9; or current smokers with the numbers of cigarettes/day: 1–10, 11–20, or >20), coffee consumption (cups/day: none, less than one, one, two to three, or more than three), alcohol consumption (drinks/day: 0, <1, 1–1.9, 2–2.9, or ≥3), general health status (excellent, very good, good, fair, or poor), BMI (in kg/m^2: 12.0–24.9, 25.0–29.9, or ≥30.0), physical activity (never/rarely, one to three times per month, one to two times per week, three to four times per week, and five or more times per week), and total energy intake (quintiles). Multivitamin users were also likely to use individual vitamin supplements, and considerable amounts of micronutrients form individual supplements may affect our primary analyses on multivitamin use. We therefore conducted further analysis adjusting for the supplemental uses of individual vitamins and minerals. The statistical significance for a linear trend was tested by assigning a value to each exposure category (0 for nonusers, 0.5 for less than one time per week, two for one to three times per week, five for four to six times per week, and seven for daily users) and including it as a continuous variable in the logistic regression model. The analysis was first conducted for all study participants and then stratified by age (years: <60, 60–64, and ≥65), sex (men versus women), general health status (excellent or very good, good, and fair or poor), smoking status (never versus ever), BMI (in kg/m^2: 12.0–24.9, 25.0–29.9, or ≥30.0), and physical activity (never/rarely, more than once per month). When possible, detailed values of the stratifying variables were adjusted along with all other confounders to minimize the possibility of residual confounding.

Our primary analysis focused on multivitamin supplements. However, we also examined the use of individual vitamins and minerals in relation to diabetes. These analyses showed that vitamin C and calcium supplement use was associated with a lower risk of diabetes. Therefore, we conducted post hoc analysis to examine whether these associations were modified by the use of multivitamins (users versus nonusers) or dietary intakes of corresponding nutrients from foods (above versus below medians). All statistical

Table 1—*Population characteristics according to baseline multivitamin use in the NIH-AARP Diet and Health Study*

	Frequency of multivitamin use					
	Never*	Less than once per week	One to three times per week	Four to six times per week	Seven times per week	*P*†
n	97,134	4,584	10,729	13,588	105,972	
Age (years)	61.3 ± 5.4	60.2 ± 5.3	60.4 ± 5.4	60.4 ± 5.3	61.4 ± 5.4	<0.0001
Men (%)	64.7	53.7	53.0	53.8	53.9	0.34
Whites (%)	93.3	92.1	91.8	92.7	94.1	<0.0001
BMI (kg/m^2)	26.8 ± 4.7	26.5 ± 4.6	26.6 ± 4.8	26.5 ± 4.5	26.3 ± 4.7	<0.0001
High school education or more (%)	75.6	80.5	80.2	81.4	78.8	<0.0001
Married or couples	74.2	69.1	67.6	67.4	67.6	0.34
Physical activity (%)						<0.0001
Never/rarely	16.5	14.8	14.5	12.4	13.2	
One to three times per month	14.2	17.7	16.1	15.0	12.1	
One to two times per week	22.1	25.8	26.1	25.9	21.2	
Three to four times per week	26.8	26.5	28.0	29.8	30.1	
Five or more times per week	19.7	14.7	14.7	16.3	22.9	
Smoking (%)						<0.0001
Never	38.0	40.6	41.1	40.4	39.0	
Past smokers	50.3	46.7	46.4	48.6	51.1	
Current smokers	10.5	11.7	11.4	9.9	8.9	
Coffee consumption(%)						<0.0001
Nondrinker	10.4	9.3	9.2	9.3	10.8	
Less than one cup per day	15.3	16.7	16.9	17.2	16.8	
One cup per day	15.8	14.3	15.0	14.4	16.2	
Two or more cups per day	58.1	59.5	58.7	58.9	55.9	
Alcohol consumption (%)						0.0001
Nondrinkers	20.5	18.9	17.2	17.4	20.2	
Less than 1 drink per day	14.7	16.4	16.2	15.2	15.6	
One or more drinks per day	53.1	55.3	57.2	57.3	54.0	
Health status (%)						0.0001
Excellent or very good	59.9	58.8	58.4	60.6	60.6	
Good	31.6	32.2	33.3	31.8	31.1	
Fair or poor	7.4	7.9	7.2	6.4	7.1	
Calorie intake (kcal)	1,835 ± 650	1,797 ± 641	1,805 ± 640	1,786 ± 625	1,798 ± 631	0.15
Single supplement use (%)						
Iron	4.1	10.6	12.7	12.8	13.3	<0.0001
Zinc	7.2	13.5	14.7	16.5	18.7	<0.0001
Selenium	4.2	5.8	6.9	8.8	11.6	<0.0001
Folate	4.6	7.7	8.4	9.7	11.9	<0.0001
Vitamin A‡	5.9	16.1	17.4	17.8	17.9	0.005
β-Carotene‡	8.8	18.2	18.9	21.1	23.2	<0.0001
Vitamin C‡	22.5	57.7	55.3	57.6	60.2	<0.0001
Vitamin E‡	22.3	44.8	46.9	50.9	55.9	<0.0001
Calcium‡	16.7	48.2	48.1	49.7	51.1	<0.0001

Data are means ± SD for continuous variables and proportions for categorical variables. The numbers of missing observations are 2,076 (0.89%) for race, 4,063 (1.75%) for BMI, 4,688 (2.02%) for education, 1,176 (0.51%) for marriage, 1,505 (0.65%) for physical activity, 2,605 (1.12%) for smoking, 750 (0.32%) for coffee consumption, 25,062 (10.80%) for alcohol consumption, 2,753 (1.19%) for health status, 13,954 (6.01%) for calorie intake, and <0.2% for individual vitamin supplements. *All *P* values <0.0001 for differences of covariates between never users and all users, with the exception of health status ($P = 0.017$). †*P* values for the global differences of covariates across four frequency categories of multivitamin users only. ‡Combined four frequencies of supplement use (times/week: less than one, one to three, four to six, and daily) as yes.

analysis was performed by using SAS release 9.1 (SAS Institute, Cary, NC), and the significance tests were two tailed with $\alpha = 0.05$.

RESULTS — Of 232,007 participants (135,423 men and 96,584 women), 72,577 (53.6%) men and 62,296 (64.5%) women took multivitamin supplements. Among them, 57,119 (78.7%) men and 48,853 (78.4%) women reported daily use. Of individual micronutrient supplements, vitamin C (34.6%) was the most commonly used, followed by vitamin E (31.6%), calcium (29.4%), β-carotene (13.1%), zinc (10.5%), vitamin A (10.3%), iron (7.62%), folic acid (6.54%), and selenium (6.25%).

Table 1 summarizes baseline characteristics according to frequency of multivitamin use. Compared with nonusers of

Table 2—*ORs (95% CI) of diabetes risk according to baseline use of multivitamin in the NIH-AARP Diet and Health Study*

	Frequency of multivitamin use					
	Never	Less than once per week	One to three times per week	Four to six times per week	Seven times per week	*P* for trend
Any multivitamin						
n cases	6,483	291	626	699	6,031	
OR (95% CI)*	1.00	1.03 (0.91–1.17)	0.93 (0.85–1.01)	0.85 (0.78–0.92)	0.96 (0.92–0.99)	0.008
OR (95% CI)†	1.00	1.07 (0.94–1.21)	0.97 (0.88–1.06)	0.92 (0.84–1.00)	1.02 (0.98–1.06)	0.64
Individual multivitamin						
Stress-tab type						
n cases	12,996	119	121	97	559	
OR (95% CI)*	1.00	1.02 (0.84–1.24)	1.04 (0.86–1.25)	1.07 (0.87–1.33)	0.96 (0.88–1.05)	0.52
OR (95% CI)†	1.00	1.06 (0.87–1.28)	1.08 (0.89–1.31)	1.18 (0.95–1.46)	0.99 (0.90–1.09)	0.79
Therapeutic or theragran type						
n cases	12,131	102	144	158	1,376	
OR (95% CI)*	1.00	0.94 (0.77–1.15)	0.88 (0.74–1.04)	0.96 (0.82–1.14)	1.00 (0.95–1.06)	0.91
OR (95% CI)†	1.00	0.96 (0.78–1.18)	0.91 (0.76–1.08)	1.04 (0.88–1.23)	1.04 (0.98–1.11)	0.17
One-a-day type						
n cases	8,022	260	494	561	4,677	
OR (95% CI)*	1.00	0.97 (0.85–1.11)	0.92 (0.84–1.02)	0.84 (0.77–0.92)	0.96 (0.92–0.99)	0.006
OR (95% CI)†	1.00	0.99 (0.87–1.13)	0.94 (0.85–1.04)	0.90 (0.82–0.99)	1.00 (0.96–1.04)	0.63

*Adjusted for age, sex, race, BMI, education levels, marital status, physical activity, smoking status, coffee consumption, alcohol consumption, general health status, and total energy intake. †Further adjusted for uses of individual vitamins and minerals: yes/no: iron, zinc, selenium, and folate; frequency (never, less than one, one to three, four to six, and seven times per week): vitamin A, β-carotene, vitamin C, vitamin E, and calcium.

any multivitamins, users, in general, tended to have a slightly healthier lifestyle than nonusers. Users were more likely than nonusers to be women, white, slightly lean, physically active, drink alcohol, and be graduates with a high school degree or higher but less likely to be current smokers (all $P < 0.0001$). They were also more likely to report the use of individual supplements of vitamins and minerals than those who did not use multivitamins. Multivitamin users reported slightly healthier health status than nonusers at baseline ($P = 0.017$). The distributions of covariates across multivitamin use frequencies appeared to be more complex; for most covariates, no apparent monotonic trends were observed across frequencies of multivitamin use.

Baseline use of multivitamins in 1996–1997 was examined in relation to incident diabetes ($n = 14,130$) diagnosed after 2000 (Table 2). Compared with nonusers of multivitamin supplements, the multivariate-adjusted ORs after controlling for traditional diabetes risk factors were 1.03 (95% CI 0.91–1.17) for less than one time per week, 0.93 (0.85–1.01) for one to three times per week, 0.85 (0.78–0.92) for four to six times per week, and 0.96 (0.92–0.99) for seven or more times per week (P for trend = 0.008). However, this significant association disappeared after further adjusting for use of individual micronutrient supplements (P for trend = 0.64). Similarly, none of the individual types of multivitamins (one-a-day, theragran, and stress tab) were associated with diabetes risk, after controlling for uses of individual micronutrient supplements. We further performed several subgroup analyses by age, sex, self-assessed health status, smoking status, BMI, and physical activity to examine whether multivitamin use was associated with diabetes risk in any of these subpopulations (supplementary Table A1 in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-1260/DC1). No significant associations were observed.

In the analysis of individual vitamins and minerals (Table 3), we found statistically significant associations between the use of vitamin C or calcium and a lower risk of diabetes. Compared with nonusers, the multivariate-adjusted ORs of diabetes risk among daily users were 0.91 for vitamin C (95% CI 0.86–0.97; P for trend = 0.001) and 0.85 for calcium (0.80–0.90; P for trend <0.0001). Further analysis suggests that the association between vitamin C supplement use and diabetes risk may be limited to individuals who did not use multivitamins or had low dietary intake of vitamin C (supplementary Table A2). In contrast, the inverse association between frequent use of calcium and diabetes risk did not vary by multivitamin use or dietary intake of calcium or vitamin D. As calcium intake might likely be used by participants with low body weight for bone health who might also have a lower risk of diabetes, we further controlled in the analysis for weight change between baseline and the follow-up survey. The results were barely changed (data not shown). Finally, we found total calcium intake was also associated with lower diabetes risk, but this association appeared to be driven by calcium supplements rather than calcium intake from dietary sources (data not shown).

CONCLUSIONS — In this large cohort of older adults, we did not find an association between multivitamin use and future diabetes risk. Our data, however, suggest a lower risk of diabetes among regular users of vitamin C or calcium supplements. Because of the exploratory and observational nature of our study, potential benefit of vitamin C and calcium use on diabetes prevention should be further evaluated.

Multivitamins are widely used among U.S. adults, particularly the elderly, for potential health benefits. To the best of our knowledge, our study is the first prospective evaluation on potential benefits

Table 3—*ORs (95% CI) of diabetes diagnosed after 2000 according to baseline use of individual vitamins and minerals

	Individual supplement intake		
	Nonuser	User	*P*
Iron			
n cases	12,836	1,294	
OR (95% CI)	1.00	1.02 (0.95–1.09)	0.64
Zinc			
n cases	12,359	1,771	
OR (95% CI)	1.00	1.05 (0.98–1.13)	0.16
Selenium			
n cases	13,158	972	
OR (95% CI)	1.00	0.94 (0.86–1.03)	0.18
Folate			
n cases	13,012	1,118	
OR (95% CI)	1.00	1.02 (0.95–1.11)	0.56

	Frequency of individual supplement intake					
	Never	Less than once per week	One to three times per week	Four to six times per week	Seven times per week	*P* for trend
Vitamin A						
n cases	12,384	266	216	145	1,106	
OR (95% CI)	1.00	1.15 (0.99–1.34)	1.07 (0.91–1.26)	1.05 (0.86–1.29)	1.08 (1.00–1.18)	0.061
β-carotene						
n cases	12,003	239	281	205	1,390	
OR (95% CI)	1.00	0.96 (0.82–1.12)	1.11 (0.96–1.28)	1.01 (0.85–1.20)	1.05 (0.97–1.14)	0.17
Vitamin C						
n cases	8,762	638	559	450	3,700	
OR (95% CI)	1.00	0.95 (0.86–1.04)	0.97 (0.87–1.08)	0.89 (0.78–1.00)	0.91 (0.86–0.97)	0.0012
Vitamin E						
n cases	9,045	364	441	446	3,818	
OR (95% CI)	1.00	0.99 (0.87–1.13)	0.90 (0.80–1.02)	0.91 (0.80–1.03)	0.99 (0.93–1.04)	0.51
Calcium						
n cases	9,972	644	599	412	2,486	
OR (95% CI)	1.00	0.92 (0.84–1.01)	0.91 (0.83–1.00)	0.85 (0.76–0.95)	0.85 (0.80–0.90)	<0.0001

*Adjusted for age, sex, race, BMI, education levels, marital status, physical activity, smoking status, coffee consumption, alcohol consumption, general health status, total energy intake, any multivitamin use, and individual vitamins and minerals yes/no: iron, zinc, selenium, and folate; frequency (never, less than one, one to three, four to six, and seven times per week): vitamin A, β-carotene, vitamin C, vitamin E, and calcium, when possible.

and risks of multivitamin use in preventing type 2 diabetes. There are several explanations for the null association. First, it is likely that multivitamins at their current composition cannot reduce the risk of diabetes. Most multivitamins contain lower amounts of single antioxidants than individual vitamin supplements and thus might not be sufficient to be biologically effective. Alternatively, as multivitamins contain many vitamins and minerals, it is possible that the potential mild benefits of some micronutrients are antagonized by detrimental effects from others.

Associations between intakes or biomarkers of vitamins and minerals and diabetes risk have been examined in some epidemiological studies. For example, observational studies have found significant inverse correlations between antioxidant levels and several biomarkers of insulin resistance and/or glucose intolerance in healthy individuals (8). Antioxidant levels in the blood, such as vitamins C and E and β-carotene, were also significantly lower in individuals with type 2 diabetes than in nondiabetic control subjects (9,10). Previous prospective cohort studies consistently reported an inverse association between incidence of type 2 diabetes and dietary, serum, or plasma levels of vitamins C (11) and E (11–13) and β-carotene (11,14) among initially nondiabetic individuals. However, there have been few clinical trials on vitamin supplements for primary prevention of type 2 diabetes. Secondary analyses of randomized clinical trials on cardiovascular events and cancers found no significant effects of vitamin E or β-carotene supplementation on the incidence of type 2 diabetes (15,16). Further, one trial (17) reported no effect of homocysteine lowering by B vitamin supplements on the risk of developing type 2 diabetes. Finally, epidemiological studies (18,19) yielded inconsistent evidence on other individual micronutrient supplements (such as zinc, chromium, and selenium) and type 2 diabetes in adults.

Despite the lack of benefit of multivitamins on diabetes risk, we found that users of either vitamin C or calcium had a lower risk of diabetes than nonusers. The potential benefit of a vitamin C supplement seem to be limited to individuals who did not take multivitamins or had lower dietary intake of vitamin C, which is consistent with some evidence that suggests that dietary vitamin C intake may be

suboptimal in the U.S. general population, especially among the elderly (20). Vitamin C is a potent water-soluble antioxidant and can effectively scavenge several reactive species and regenerate tocopherols and tocotrenols from their respective radical species (20). Vitamin C may also have a role in the energy-dependent release of insulin from pancreatic islets (21). Some small and short-term randomized trials have been conducted among patients with type 2 diabetes; some reported that vitamin C supplementation (1–2 g/day) reduced oxidative stress and improved endothelial function in diabetic patients (20). Further, a recent trial has shown suggestive evidence for vitamin C (500 mg/day) in preventing type 2 diabetes among women at high risk of cardiovascular disease (16). Because of limited data from randomized trials, our observational evidence of a potential benefit of vitamin C supplementation in diabetes prevention should serve as a stimulus for further investigation.

We found a consistent association of calcium supplementation with lower diabetes risk. It is difficult to argue that such residual confounding was specific to calcium but not to multivitamins or other micronutrient supplements. On the other hand, it is plausible that a potential beneficial effect of calcium on diabetes is partially mediated by its effects on blood pressure (22), insulin sensitivity (23), and body weight (24). Recently, animal and human studies indicated that high calcium intake might decrease levels of parathyroid hormone and 1,25(OH)2 vitamin D (calcitriol) and thus influence adipocyte metabolism by inhibiting lipogenesis and stimulating lipolysis (25). Moreover, the biological effects of calcium may well depend on the presence or absence of other highly correlated nutrients, especially vitamin D. Our results did not show that dietary vitamin D intake modified the association between calcium supplement use and type 2 diabetes. Because of the lack of information on vitamin D contents in multivitamin supplements and the relatively low proportions of vitamin D supplement use, we cannot address the comparative importance of calcium and vitamin D in the observed associations. Further, we found no evidence for the association between calcium intake from diet alone and diabetes risk. Therefore, we cannot entirely exclude the possibility that the association between calcium supplement use and diabetes could be explained by unmeasured confounding.

Major strengths of the current study include its large sample size, prospective study design, detailed measures of epidemiologic profiles, and thorough statistical analyses. Our study also has several limitations. First, in such a large cohort, we had to rely on self-reported diagnoses rather than annual glucose tolerance screening to identify diabetic patients. If participants with undiagnosed diabetes or prediabetic status used vitamin supplements more or less frequently than did truly healthy participants, the risk estimates might have been biased. To minimize this possibility, we only included diabetes cases diagnosed after 2000 in the current analyses. Second, information on vitamin/mineral supplement use was self-reported and therefore misclassifications are likely. The exposure misclassification was likely nondifferential with respect to the outcome and might thus have attenuated the true relationships. Third, we did not collect data on the duration of multivitamin use and the frequency over the follow-up period to account for time-varying effects. Finally, although we have controlled for and stratified by a variety of potential confounders, the study is observational in nature and we could not exclude the possibility of chance or residual confounding from unmeasured or inadequately measured confounders.

In conclusion, this large prospective study among U.S. older adults provides evidence against use of multivitamin supplements for diabetes prevention. Our preliminary findings on lower diabetes risk among users of vitamin C and calcium supplements are intriguing and should be followed-up in future investigations.

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Y.S. conceived and designed the study, researched data, and wrote the manuscript. Q.X. researched data, wrote the manuscript, and reviewed/edited the manuscript. Y.P., A.H., and A.S. contributed to data collection, the discussion, and reviewed/edited the manuscript. H.C. researched data, wrote the manuscript, contributed to the discussion, and reviewed/edited the manuscript.

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